Remarks

A. *Status of the Claims*

Claims 67-68, 73, 100-102, and 104-130 were pending at the time of the Action. Claim 67 has been amended. Support for the amendment to claim 67 can be found in the specification at, for example, p. 8, ln. 21-28, and p.41, ln. 12-24. Claim 73 has been amended to delete redundancy with claim 67. New claims 131-134 have been added. Support for the new claims can be found in the specification at, for example, p. 8, ln. 21-28; p. 24, ln., 9, to p. 25, ln. 18; and p. 41, ln. 12-24. Claims 67-68, 73, 100-102, and 104-134 are now pending.

B. *The Claims are Enabled*

The Action rejects claims 67-68, 73, 100-102, and 104-130 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Action asserts that an analysis of the specification in accordance with the *Wands* factors demonstrates that it would require undue experimentation for a person of ordinary skill in the art to practice the claimed invention. However, contrary to the Action's assertions, an analysis of the *Wands* factors demonstrates that a person of ordinary skill in the art could make and use the claimed invention without undue experimentation.

As discussed in detail below, a person of ordinary skill in the art could make and use the claimed invention without undue experimentation in view of:

- the rat and mouse animal model studies in the specification showing the role of ACE2 in cardiac, lung, and kidney diseases;
- the disclosed similarities of the rat, mouse, and human ACE2 structure and function;
- the teaching in the specification that an ACE2 decreased state, such as cardiac, lung, and kidney disease, may be treated by administering to an animal in need thereof an effective amount of an ACE2 polypeptide.

The enablement of the claims is further confirmed by:

- the demonstration by Imai *et al.* that injecting ACE2 knockout mice or acid-treated wild-type mice with a human ACE2 protein protected the mice from severe acute lung injury (*see* Neu Declaration, para. 14);
- the showing of a therapeutic benefit of administration of a human ACE2 polypeptide in a porcine ARDS model (*see* Neu Declaration, para. 11; Schuster Declaration, para. 17-37);
- the showing of a therapeutic benefit of administration of a human ACE2 polypeptide in a porcine pulmonary hypertension model (Schuster Declaration, para. 14);
- the showing of a therapeutic benefit of administration of a human ACE2 polypeptide in a mouse cardiovascular disease model (Schuster Declaration, para. 13-14); and
- the showing of a therapeutic benefit of administration of a human ACE2 polypeptide in a mouse kidney disease model (Schuster Declaration, para. 15-16).

In view of these results from two different mammalian species administered an ACE2 polypeptide from a third mammalian species to treat ACE2 decreased states in multiple organs, it is clear that the full scope of the claimed invention is enabled.

It is further noted that although the Action states that the Schuster Declaration was considered (Action, p. 2), this does not appear to be the case because the Action is void of any discussion of the Schuster Declaration. The Examiner is reminded that "A declaration or affidavit is, itself, evidence that must be considered." MPEP § 2164.05 (emphasis in original). In fact, the MPEP encourages Applicants to provide evidence to demonstrate that the disclosure enables the claimed invention (MPEP § 2164.05). "Once that evidence is submitted, it must be weighed with all other evidence according to the standards set forth above so as to reach a determination as to whether the disclosure enables the claimed invention." MPEP § 2164.05 (emphasis added). Accordingly, the Examiner must consider the evidence presented in the Schuster Declaration.

1. The Breadth of the Claims and the Nature of the Invention

Current claim 67 is directed to a method of treating an ACE2 decreased state comprising identifying an ACE2 decreased state in a mammal having hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease, and administering to the mammal a therapeutically effective amount of an ACE2 polypeptide, wherein the ACE2 decreased state is treated.

Current claim 108 is directed to a method of treating a lung disease comprising administering to a mammal having a lung disease a therapeutically effective amount of an ACE2 polypeptide, wherein the lung disease is treated.

Current claim 116 is directed to a method of treating a cardiovascular disease comprising administering to a mammal having a cardiovascular disease a therapeutically effective amount of an ACE2 polypeptide, wherein the cardiovascular disease is treated.

Current claim 125 is directed to a method of treating a kidney disease comprising administering to a mammal having a kidney disease a therapeutically effective amount of an ACE2 polypeptide, wherein the kidney disease is treated.

2. The State of the Art and the Level of Ordinary Skill in the Art

The use of protein therapy in the treatment of diseases is well-known in the medical field (Neu Declaration, para. 6). Examples of such protein therapies are described in the publication *Scientific Considerations Related to Developing Follow-On Protein Products*, 2004, which is cited in the Action at page 9. This publication mentions such drugs as Epogen®, which is a protein therapy based on human erythropoietin; and Neupogen®, which is a protein therapy based on granulocyte colony-stimulating factor. As pointed out in the Action, *Scientific Considerations Related to Developing Follow-On Protein Products* also notes that six companies manufacture FDA-approved versions of human growth hormone (paragraph bridging pages 5-6).

Thus, protein therapy was well-known and commercially successful in the art and the level of skill was high.

The Examiner notes that the half lives of six, FDA-approved human growth hormone drugs vary from 1.75 to 10 hours (Action, p. 9). From this, the Examiner concludes that "such large variations can impact the effectiveness of the product and the as [sic] the body's immune response to it." (Action, p. 9). The Examiner is reminded, however, that all six of the human growth hormone products are FDA approved. Evaluating the safety and effectiveness of a particular drug for human use is the responsibility the FDA not the USPTO. Here, the FDA approved all six of the human growth hormone drugs even though their half lives varied from 1.75 to 10 hours. Thus, the Examiner's conclusion on this issue clearly does not follow from the facts.

Despite the fact that protein therapy in the treatment of diseases was well-known in the medical field, the Action asserts that the state of the art in protein therapy was unpredictable (Action, p. 6). In particular, the Action states that the artisan could not reasonably predict that any protein could be delivered in any cell of any mammal at therapeutic effective levels (Action, p.6). The Action's assertion, however, fails to consider the characteristics of the ACE2 protein. The active ACE2 enzyme is a secreted protein. This was known by those in the art at the time the present application was filed (*see e.g.,* Donoghue *et al.*, Circulation Research (2000)). Thus, the Action's concern with getting the protein into cells is unfounded. Moreover, the Action makes several references to the unpredictability of "expressing" the protein in the mammal. The reason for these statements is unclear because the current claims are directed to administering an ACE2 polypeptide. Thus, these arguments fail to support the present rejection.

Furthermore, the evolutionary conservation of ACE2 structure and activity among mammals, as well as other organisms, is further evidence that the currently claimed method could be practiced in any mammal (*see e.g.,* Specification, FIGs. 1A, showing an alignment of the amino acid sequences of ACE2 from human, rat, and mouse, which illustrates the identities and similarities between these sequences). In addition, results in flies showed that a P-element mutation associated with the ACE homologue, ACER, results in a severe and lethal defect of heart morphogenesis providing further evidence that ACE/ACE2 functions in the heart have been conserved through evolution (Specification, p. 30, ln. 28 to p. 31, ln. 2). The previously cited publication entitled "Structure, Evolutionary Conservation, and Function of Angiotensin- and Endothelin-Converting Enzymes" (Macours *et al.*, *International Review of Cytology*, 239:47-97 (2004)), is further evidence of the conservation of the ACE/ACE2 system.

Furthermore, the specification discloses that AngI and AngII are substrates for ACE2, which functions as a carboxypeptidase to cleave a single residue from each of AngI and AngII (p. 2, ln. 5-10). Applicants also provided previously the results of a BLAST search of the ACE2 substrate, AngII, which shows that AngII is present in numerous mammals including *Pan troglodytes, Mus musculus, Homo sapiens, Callithrix jacchus, Gorilla gorilla, Canis familiearis, Macaca mulatta, Rattus norvegicus, Ovis ammon,* and *Pongo pygmaeus*. In view of the evidence that ACE2 structure and function is conserved among mammals, one would expect that the currently claimed method could be practiced in any mammal (*see* Neu Declaration, para. 5).

The Action cites Acton *et al.* (US 6,194,556) as providing a contradictory teaching as to the function of ACE2. However, Acton's prediction of the function of ACE2 was proven wrong by the studies disclosed in the present specification. The studies in the specification have been

confirmed by at least Imai *et al.*, the Neu Declaration, and the Schuster Declaration. The Action's continued reliance on Acton is improper.

The Action also undertakes a lengthy discussion of the unpredictability of using liposomes as delivery vehicles (Action, p. 8-9). Although the current claims use open claim language, and thus would encompass a method in which liposomes also were administered, there is no recitation of or requirement for liposomes in the current claims. Moreover, liposomes were not used as delivery vehicles in the animal model studies described in the Neu and Schuster Declarations (discussed below). Thus, the Action's arguments regarding liposomes also fail to support the present rejection.

Furthermore, many of the Action's arguments and evidence of unpredictability pertain to safety and efficacy issues (*see* Final Action, p. 9-10). In particular, the Action points to references teaching the importance of dosing, clearance and efficacy of the product, preclinical evaluation for toxicity and immunogenicty. The MPEP states, however, that an applicant need not demonstrate that the invention is completely safe (MPEP § 2164.01(c)). Furthermore, testing for the full safety and effectiveness of a particular drug for human use is more properly left to the Food and Drug Administration (FDA). *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995). "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." *Id.* The stage at which an invention in the pharmaceutical field becomes useful is well before it is ready to be administered to humans. *Id.* Moreover, there is nothing in the patent statute or any other statutes that gives the Patent Office the right or the duty to require an applicant to prove that compounds he is claiming, and which he has stated are useful for "pharmaceutical applications," are safe,

effective, and reliable for use with humans. *In re Krimmel*, 292 F.2d 948, 954 (C.C.P.A. 1961); *see also* MPEP § 2164.01(c).

The Examiner has the initial burden of producing reasons that substantiate a rejection based on lack of enablement. The Action's generalizations about clinical safety and efficacy fail to satisfy this burden. Furthermore, even if the Examiner had shifted the burden on enablement, the Examiner's allegations of unpredictability and undue experimentation are rebutted by the showing that a recombinant human ACE2 protein protected mice having a decreased ACE2 state from severe acute lung injury (Imai *et al.*, p. 112, col. 2; Figures 2(d)-(f)) in a study that employed the same ACE2 knockout mouse model described in the present specification, the same lung elastance assay described in the specification (*see* p. 40, ln. 12-20), and a route of administration (intraperitoneal injection) disclosed in the specification (*see* p. 21, ln. 27-30).

The Examiner's allegations of unpredictability and undue experimentation are also rebutted by: (1) the showing of a therapeutic benefit of administration of a human ACE2 polypeptide in a porcine ARDS model (*see* Neu Declaration, para. 11; Schuster Declaration, para. 17-37); (2) the showing of a therapeutic benefit of administration of a human ACE2 polypeptide in a porcine pulmonary hypertension model (Schuster Declaration, para. 14); (3) the showing of a therapeutic benefit of administration of a human ACE2 polypeptide in a mouse cardiovascular disease model (Schuster Declaration, para. 13-14); and (4) the showing of a therapeutic benefit of administration of a human ACE2 polypeptide in a mouse kidney disease model (Schuster Declaration, para. 15-16), which are discussed below.

As stated in the Neu Declaration: "Since ACE2 is an endogenous protein in mammals and the present specification discloses the physiological role of ACE2, it would require only routine clinical studies to administer a therapeutically effective amount of an ACE2 polypeptide

to an mammal having hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease, in order to treat the mammal as recited in the current claims." (Neu Declaration, para. 6). This was demonstrated to be the case in the five different animal models mentioned above.

3. The Guidance Provided by the Specification

The present specification provides sufficient guidance to enable a person of ordinary skill in the art to make and use the claimed invention without undue experimentation. This is further supported by the studies described in the Neu and Schuster Declarations, which provide evidence that, by following the teachings in the specification, someone skilled in the art can make and use the claimed invention without undue experimentation.

The present specification provides a new paradigm for the regulation of the renin-angiotensin system. The present specification discloses that hypertension, as well as other cardiac, lung, and kidney diseases are associated with an ACE2 decreased state (*see e.g.,* p. 2, ln. 28 to p. 3, ln. 6). In particular, the rat and mouse studies in the present specification demonstrate that an ACE2 decreased state is associated with cardiovascular, renal, and lung diseases. For example, decreased ACE2 mRNA and protein levels were observed in the kidneys of hypertensive rats (Specification, p. 32, ln. 21 – p. 33, ln. 22). In studies on the ACE2 knockout mouse, it was observed that loss of ACE2 leads to detrimental effects in the kidneys (p. 36, ln. 8-11), heart defects (p. 36, ln. 14 – p. 38, ln. 12), and increases the susceptibility of the lungs to injury (p. 40, ln. 12-20).

The specification further showed in the ACE/ACE2 double knockout mice, that ablation of ACE expression on an ACE2 deficient background abolished the heart failure phenotype of ACE2 single knockout mice (specification p. 29, first paragraph and p. 38, last paragraph). This shows that only the expected ACE2 activity on the polypeptides of the RAS systems (angiotensin

I and angiotensin II conversion) was observed in the animal model. This refutes the Action's assertion that the interpretation of the results from this animal model could have been confounded by an amalgam of phenotypes and/or compensatory systems (Action, p. 12).

Accordingly, those of ordinary skilled in the art would have appreciated the therapeutic benefit of a method of treating an ACE2 decreased state comprising administering to a mammal having hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease, a therapeutically effective amount of an ACE2 polypeptide.

Moreover, enablement must be assessed from the position of a person of ordinary skill in the art. Acton *et al.* (US 6,194,556), which is cited in present specification (p. 2, ln. 11) and in the Action (*see e.g.,* p. 8), shows that ACE2 was fully available to those in the art at the time the present application was filed as a nucleotide sequence, as well as in vectors and plasmids for ACE2 expression (*e.g.* '556 patent, column 29, lines 15 to column 30 line 52). Polypeptides of ACE2 are disclosed in the '556 patent from column 30 to column 37 line 26. In addition, pharmaceutical preparations and formulations of ACE2 are disclosed in the '556 patent at column 61 line 37 to column 36 line 37. The present specification on page 18, third paragraph, even cites to the '556 patent's corresponding Canadian patent CA 2,372,387 as describing methods by which ACE2 may be produced. A further document cited in the present specification on page 18, third paragraph, is Nichols *et al.* (JBC 277 (17):14838-14843 (2002)). Nichols shows an assay for ACE2 activation based on its proteolytic activity on small peptides. Thus, those of ordinary skill in the art would have been able to make and use ACE2 polypeptides without undue experimentation in view of the teachings in the specification and the knowledge in the art.

4. The Neu Declaration

As discussed in the previously submitted declaration of Dr. Nikolaus Neu ("Neu Declaration"), Imai *et al.* (*Nature*, 436:112-116 (2005); IDS reference C61)) is further evidence that those of skill in the art can make and use the claimed invention without undue experimentation (*see* Neu Declaration, para. 7). Imai *et al.* demonstrated that injecting ACE2 knockout mice or acid-treated wild-type mice with a recombinant human ACE2 protein protected the mice from severe acute lung injury (p. 112, col. 2; Figures 2(d)-(f)). This study employed the same ACE2 knockout mouse model described in the present specification, the same lung elastance assay described in the specification (*see* p. 40, ln. 12-20), and a route of administration (intraperitoneal injection) disclosed in the specification (*see* p. 21, ln. 27-30). Thus, Imai *et al.* demonstrate that those of skill in the art can treat an ACE2 decreased state by administering a therapeutically effective amount of an ACE2 polypeptide (Neu Declaration, para. 7). The results of Imai *et al.* also provide additional evidence of the conserved function of ACE2 and the renin-angiotensin system by virtue of the fact that a human ACE2 protein was able to complement ACE2 function in mice (Neu Declaration, para. 7).

In another study described in the Neu Declaration, recombinant human soluble ACE2 (rhACE2) protein was studied in a piglet acute respiratory distress syndrome (ARDS) model (Neu Declaration, para. 8). The study was conducted by Alexander Löckinger and Benedikt Treml of Dr. Neu's research group, with the pharmacological evaluation being carried out by Manfred Schuster and Hans Loibner of Apeiron Biologics (Neu Declaration, para. 8). In this study, an ACE2 polypeptide, rhACE2, was administered as a central venous bolus injection at a dose of 100 μg/kg following the last LPS bolus injection and 120 minutes from the start of the continuous LPS infusion (Neu Declaration, para. 9). Intravenous injection is a route of administration disclosed in the present specification (*see* Specification, p. 21, ln. 27-30; Neu

Declaration, para. 9). The rhACE2 bolus injections were well tolerated and did not show any apparent side effects (Neu Declaration, para. 9). Treatment with rhACE2 stabilized or even decreased slightly pulmonary arterial pressure (PAP), while the control group showed a nearly 15% increase in PAP (Neu Declaration, para. 11). Systolic arterial pressure (SAP) was also measured. The control group showed an increase in SAP up to 12%, whereas after rhACE2 injection a stabilization and 5% decrease in SAP was observed (Neu Declaration, para. 11). The difference between the control and rhACE2 treatment groups was significant (Neu Declaration, para. 11).

In addition, oxygen concentration was measured in arterial and venous blood samples taken from the piglets every 30 minutes (Neu Declaration, para. 12). There was a potential stabilization observed of arterial as well as venous oxygen concentration in the group receiving rhACE2, however the data did not reach statistical significance in this study and will have to be confirmed in further experiments (Neu Declaration, para. 12). The results of this study also provide additional evidence of the conserved function of ACE2 and the renin-angiotensin system by virtue of the fact that a human ACE2 protein was used to treat pigs.

In view of the *in vivo* rat and mouse data on the role of ACE2 in cardiac, lung, and kidney diseases; the disclosed similarities of the rat, mouse, and human ACE2 sequences; and the knowledge in the art of ACE2 sequences, expression constructs, and formulations; those of ordinary skill in the art could have practiced the claimed method in a multitude of mammals including humans. This is confirmed by the studies described in Imai *et al.* and in the Neu Declaration.

5. The Schuster Declaration

As further evidence of the enablement of the current claims, Applicants previously provided the declaration of Dr. Manfred Schuster ("Schuster Declaration"). Although page 2 of

the Action states that the Schuster Declaration was considered by the Examiner, this does not appear to be the case because the Action is void of any discussion of the Schuster Declaration. Applicants, therefore, request that the Examiner consider the extensive evidence presented in the Schuster Declaration.

Dr. Schuster is the Head of Research and Development at Apeiron Biologics, which is the licensee of the present patent application. The Schuster Declaration describes four studies on therapeutic uses of recombinant human soluble ACE2 (rhACE2) protein performed under Dr. Schuster's direction at Apeiron Biologics and in collaboration with researchers at University Hospital Innsbruck (Schuster Declaration, para. 2). Specifically, these studies describe the use of rhACE2 in treating: (1) cardiovascular complications in mice; (2) pulmonary hypertension in pigs; (3) kidney disease in mice, and (4) acute respiratory distress syndrome in pigs (Schuster Declaration, para. 2).

The Schuster Declaration states that the studies of the rhACE2 protein were pursued because of the disclosure in the present specification that ACE2 was a critical negative regulator of the renin-angiotensin system (RAS) and that the activation of ACE2 could be used to treat hypertension, cardiac disease, kidney disease, and lung disease (Schuster Declaration, para. 4). Based on teachings in the specification, a recombinant human ACE2 (rhACE2) protein was produced and provided in a physiological buffer for use in these studies (Schuster Declaration, para. 5 and 6). The recombinant human ACE2 protein used in the studies is referred to interchangeably in the Schuster Declaration as rhACE2 and APN 01 (Schuster Declaration, para. 5).

a) Cardiovascular Complications in Mice

The Schuster Declaration states that by following the teachings in the present specification it was demonstrated that rhACE2 can treat cardiovascular complications in mice

(Schuster Declaration, para. 5). In particular, the Schuster Declaration (para. 7) noted teachings in the specification that: (1) ACE2 is a critical negative regulator of the renin-angiotensin system (RAS) (Specification, paragraph bridging pages 2-3); (2) ACE2 cleaves angiotensin I (Ang I) to generate Ang 1-9, and it cleaves angiotensin II (Ang II) to generate Ang 1-7 (Specification, p. 29, ln. 10-16) (*see also* Exhibit 2, Figure 1); (3) loss of ACE2 resulted in an increase in Ang II and led to detrimental heart defects in the ACE2 knockout mouse (Specification, p. 36, ln. 14 – p. 38, ln. 26); (4) an ACE2 decreased state, such as cardiac disease, may be treated by administering to an animal in need thereof an effective amount of an agent that can increase the expression of ACE2 (Specification, p. 9, ln. 10-15); (5) the agent that increases the expression of ACE2 may be an ACE2 protein (Specification, p. 9, ln. 16-25); and (6) the agent may be administered to a subject via intravenous injection or intraperitoneal injection (Specification, p. 21, ln. 27-30). Accordingly, rhACE2 was administered either by intravenous injection or intraperitoneal injection to: (1) healthy Balb-c mice, (2) healthy Balb-c mice administered Ang II, (3) Balb-c mice and ACE2 knock-out Balb-c mice subjected to aortic banding heart failure, and (4) Balb-c mice subjected to coronary ligation ischemia (Schuster Declaration, para. 7).

The results of the study using rhACE2 to treat cardiovascular complications in mice showed that ACE2 therapy reduced heart beat rate and increased heart efficiency, neutralized or significantly reduced the negative effects of elevated Ang II, relieved the symptoms of aortic banding in ACE2 knock-out mice, and provided a therapeutic benefit in myocardial infarction (Schuster Declaration, para. 12; *see also* para. 8-11).

b) Pulmonary Hypertension in Pigs

The Schuster Declaration states that by following the teachings in the present specification it was demonstrated that rhACE2 can treat pulmonary hypertension in pigs. In

particular, the Schuster Declaration (para. 13) noted teachings in the specification that: (1) ACE2 cleaves angiotensin I (Ang I) to generate Ang 1-9, and it cleaves angiotensin II (Ang II) to generate Ang 1-7 (Specification, p. 29, ln. 10-16) (*see also* Exhibit 2, Figure 1); (2) the specification discloses that ACE2 is expressed in the lung (Specification, p. 40, ln. 11-12); (3) loss of ACE2 resulted in increased sensitivity to lung injury in the ACE2 knockout mouse (Specification, p. 36, ln. 14 – p. 38, ln. 26); (4) an ACE2 decreased state, such as lung disease, may be treated by administering to an animal in need thereof an effective amount of an agent that can increase the expression of ACE2 (Specification, p. 9, ln. 10-15; p. 40, ln. 18-20); (5) the agent that can increase the expression of ACE2 can be an ACE2 protein (Specification, p. 9, ln. 16-25); and (5) the agent may be administered to a subject via intravenous injection (Specification, p. 21, ln. 27-30). Accordingly, the effects of rhACE2 administered by intravenous injection to piglets ventilated using a hypoxic gas mixture were studied (Schuster Declaration, para. 13).

The results of this study demonstrated that the treatment was well tolerated without any signs of side effects or toxicity (Schuster Declaration, para. 14). In addition, the results indicated a therapeutic benefit of administering ACE2 in pulmonary hypertension as evidenced by the significant decrease in mean pulmonary arterial pressure in animals treated with rhACE2 (Schuster Declaration, para. 14).

c) Kidney Disease in Mice

The Schuster Declaration states that by following the teachings in the present specification it was demonstrated that rhACE2 can treat diabetic nephropathy in mice (Schuster Declaration, para. 15). In particular, the Schuster Declaration (para. 15) noted teachings in the specification that: (1) ACE2 is expressed in the kidney (Specification, p. 35, ln. 9-10); (2) loss of ACE2 resulted in enhanced Ang II signaling which ultimately mediated detrimental effect in

the kidneys of the ACE2 knockout mouse (Specification, p. 35, ln. 9 to p. 36, ln. 11); (3) an ACE2 decreased state, such as kidney disease, may be treated by administering to an animal in need thereof an effective amount of an agent that can increase the expression of ACE2 (Specification, p. 9, ln. 10-15); (4) the agent that can increase the expression of ACE2 may be an ACE2 protein (Specification, p. 9, ln. 16-25); and (5) the agent may be administered to a subject via intraperitoneal injection (Specification, p. 21, ln. 27-30). Accordingly, rhACE2 was administered by intraperitoneal injection to mice with diabetic nephropathy (Schuster Declaration, para. 15 and 16).

Kidney function was assessed by measuring albumin excretion in urine (Schuster Declaration, para. 16). The results of this study showed that albumin excretion in urine due to kidney damage was reduced significantly compared to a control group following 4 weeks of treatment with rhACE2 (Schuster Declaration, para. 16). These findings confirm a therapeutic benefit of ACE2 in diabetic nephropathy (Schuster Declaration, para. 16).

d) Acute Respiratory Distress in Pigs

The Schuster Declaration also provides an update on the study previously described in the Neu Declaration. As noted in both the Schuster Declaration and the Neu Declaration, this study is a collaboration between researchers at Apeiron Biologics and University Hospital Innsbruck. The ARDS animal model provides reproducible conditions in which to evaluate the effects of administrated drugs (Schuster Declaration, para. 36). A variety of pharmacological and physiological parameters were evaluated over the course of the study (*see* Schuster Declaration, para. 18-36). The results of the study in the ARDS piglet model demonstrate the ACE2 therapy is well tolerated and provides a therapeutic benefit (Schuster Declaration, para. 25 and 37). In particular, the study demonstrated that ACE2 therapy increased lung function and

improved kidney function in the ARDS piglet model (Schuster Declaration, para. 37; *see also* para. 18-36).

Further studies in the ARDS piglet model were performed to further elucidate the mechanism behind the therapeutic effects of ACE2 treatment (Schuster Declaration, para. 49). The drug Telmisartan, which blocks AngII signaling via the AT1 receptor, was administered alone or in combination with rhACE2 to see if the therapeutic effects of the ACE2 treatment were related to reduced Ang II signaling via AT1 receptor or if other, AT1-independent effects, were responsible for the therapeutic benefit (Schuster Declaration, para. 49). The Schuster Declaration reports that the therapeutic benefit of an ACE2 therapy does not appear to be mediated only by the reduction of AT1 related signaling caused by lowered Ang II titers (para. 49).

e) Summary

In summary, the Schuster Declaration shows that by following the teachings in the present specification, one can make and use the full scope of the claimed invention without undue experimentation. In particular, the Schuster Declaration demonstrates that a therapeutically effective amount an ACE2 polypeptide has a beneficial effect in treating: (1) cardiovascular complications, (2) pulmonary hypertension, (3) kidney disease, and (4) acute respiratory distress syndrome (Schuster Declaration, para. 51). Moreover, these beneficial effects were demonstrated in two mammalian species, mice and pigs (Schuster Declaration, para. 51). Additionally, the beneficial effects achieved in mice and pigs resulted from administering a human ACE2 polypeptide (Schuster Declaration, para. 51). Thus, in view of these results from two different mammalian species administered an ACE2 polypeptide from a third mammalian species, the Schuster Declaration states that one would expect that ACE2 decreased states could

similarly be treated in any mammal (Schuster Declaration, para. 51). As discussed above, this is also confirmed by the studies described in Imai *et al.* and in the Neu Declaration.

6. The Existence of Working Examples

The Action asserts that the working examples in the specification demonstrate the role of ACE2, but do not demonstrate any method of treating any condition by administering any composition of ACE2. Compliance with the enablement requirement, however, turns on whether the invention is disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. MPEP § 2164.02. As discussed above, the present invention provides working examples showing that an ACE2 decreased state is associated with cardiovascular, renal, and lung diseases (*see* Specification, p. 32, ln. 21 – p. 33, ln. 22; p. 36, ln. 8 – p. 38, ln. 12; p. 40, ln. 12-20). Accordingly, those of ordinary skilled in the art would have appreciated the therapeutic benefit of treating an ACE2 decreased state by administering to a mammal a therapeutically effective amount of an ACE2 polypeptide. The specification provides the sequences of human, rat, and mouse ACE2 DNA and polypeptides (FIG. 1a, 10, and 11). The specification also discloses routes of administration and dosages at, for example, page 21, line 27 to page 22, line 17.

As described in the preceding sections, Imai *et al.* demonstrated that one skilled in the art is be able to practice the claimed invention without an undue amount of experimentation by demonstrating that a recombinant human ACE2 protein protected mice having a decreased ACE2 state from severe acute lung injury (p. 112, col. 2; Figures 2(d)-(f)) in a study that employed the same ACE2 knockout mouse model described in the present specification, the same lung elastance assay described in the specification (*see* p. 40, ln. 12-20), and a route of administration (intraperitoneal injection) disclosed in the specification (*see* p. 21, ln. 27-30) (*see also* Neu Declaration, para. 7). The enablement of the currently claimed invention is further confirmed by

the study in the piglet ARDS model discussed above and described in the Neu Declaration (para. 8-12) and Schuster Declaration (para. 17-37) and in the mouse cardiovascular disease model and the mouse kidney disease model described in the Schuster Declaration at paragraphs 13-14 and 15-16.

7. Summary

In view of the rat and mouse animal model studies in the specification showing the role of ACE2 in cardiac, lung, and kidney diseases; the disclosed similarities of the rat, mouse, and human ACE2 structure and function; and the teaching in the specification that an ACE2 decreased state, such as cardiac, lung, and kidney disease, may be treated by administering to an animal in need thereof an effective amount of an agent that can increase the expression of ACE2; a person of ordinary skill in the art could make and use the currently claimed invention without undue experimentation (*see* Neu Declaration, para. 14; *see also* Schuster Declaration, para. 51). The enablement of the claims is confirmed by the demonstration by Imai *et al.* that injecting ACE2 knockout mice or acid-treated wild-type mice with a rhACE2 protein protected the mice from severe acute lung injury; and the study in the piglet ARDS model showing that rhACE2 protein therapy stabilized or even decreased both pulmonary arterial pressure and systolic arterial pressure (*see* Neu Declaration, para. 14). The enablement of the claims is further confirmed by the studies described in the Schuster Declaration, which demonstrate that a therapeutically effective amount an ACE2 polypeptide has a beneficial effect in treating cardiovascular complications, pulmonary hypertension, kidney disease, and acute respiratory distress syndrome. The Schuster Declaration concludes that in view of these results from two different mammalian species administered an ACE2 polypeptide from a third mammalian species, one would expect that ACE2 decreased states could similarly be treated in any mammal (Schuster Declaration, para. 51).

The current claims are, therefore, enabled. Thus, Applicants respectfully request the withdrawal of this rejection.

8. Claims 100-131

In addition to the arguments presented above, Applicants assert that claims 100-131 are enabled for at least the following reasons.

The Action's arguments regarding the enablement rejection are directed to the breadth of the claims; the alleged lack of guidance in the specification; the alleged lack of working examples; and the alleged unpredictability of protein therapy. In particular, the Action asserts that it would require undue experimentation for a person of ordinary skill in the art to practice the claimed method in any mammal to treat a genus of ACE2 decreased states (Final Action, para. spanning pages 4-5). As discussed above, it is Applicants' position that the Action's arguments fail to establish a lack of enablement against any of the claims in view of Applicants' evidence of enablement in regard to two different mammalian species (pig and mouse) using an ACE2 polypeptide from yet a third mammalian species (human), and in view of Applicants' evidence of enablement in regard to a number of ACE2 decreased states (generally, lung disease, cardiovascular disease, and kidney disease). The Action's arguments are even less availing in regard to claims 100-131 for the reasons discussed below.

While claim 67 is directed to a method of treating an ACE2 decreased state, claim 100 is directed to a mammal having lung disease. Additionally, claims 108-115 are directed to a method of treating lung disease, claims 116-124 are directed to a method of treating cardiovascular disease, and claims 125-130 are directed to a method of treating kidney disease. Applicants further note that claims 112, 121, and 127 specify that the mammal is a human and new claim 131 recites that the ACE2 protein is a human ACE2 protein. Accordingly, the

Action's assertions regarding the treatment of any mammal having a genus of ACE2 decreased states, does not specifically address the scope of claims 100-108.

In view of the animal model studies in the specification showing the role of ACE2 in lung diseases, cardiovascular diseases, and kidney diseases; the disclosed similarities of the rat, mouse, and human ACE2 structure and function; and the teaching in the specification that lung disease, cardiovascular disease, and kidney disease may be treated by administering to an animal in need thereof an effective amount of an agent that can increase the expression of ACE2; a person of ordinary skill in the art could make and use the currently claimed invention recited in claims 100-130. This is confirmed in studies of five different mammalian model systems – the ACE2 knockout mice and acid-treated wild-type mice described by Imai *et al.,* the piglet ARDS model described in the Neu Declaration and the Schuster Declaration, the piglet pulmonary hypertension model described in the Schuster Declaration, the mouse cardiovascular disease model described in the Schuster Declaration, and the mouse kidney disease model described in the Schuster Declaration.

9. New Arguments in the Action

On page 16 of the Action, at the end of the section on the enablement rejection, there is a paragraph with the heading "New Arguments." In this paragraph, the Examiner appears to be alleging that because of the use of the term "therapeutically" in the claims, the claimed method amounts to a "cure" of all of the diseases encompassed by the claims. This "interpretation" is without merit. Claim terms are normally given there ordinary meaning. The dictionary definition of "therapeutic" is "of or relating to the treatment of disease or disorders by remedial agents or methods" (*see* Merriam-Webster Online Dictionary). As explained in the specification, "The term 'treatment or treating' as used herein means an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but

are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. 'Treating' can also mean prolonging survival as compared to expected survival if not receiving treatment." Thus, the Action's interpretation of the claims is improper because it is inconsistent with the plain language of the claims and the ordinary meaning of the claim terms.

C. *The Claims are Definite*

1. Claims 67-68, 73, and 100-107

The Action rejected claims 67-68, 73, and 100-107 under 35 U.S.C. § 112, second paragraph, as being indefinite because it is allegedly unclear what the phrase "ACE2 decreased state" means. Applicants traverse this rejection.

Claims must be read in light of the disclosure in the specification. The specification specifically discloses that an "ACE2 decreased state" is when levels of ACE2 are less than wild type levels (page 8, lines 21-28). Also as disclosed in the specification, wild type levels of ACE2 and decreased levels of ACE2 will be readily apparent to those skilled in the art using methods such as Northern blot analysis, Western blot analysis, and genetic analysis (page 8, lines 21-28; p. 24, line, 9, to p. 25, ln. 18; p. 41, ln. 12-24). Accordingly, the term "ACE2 decreased state" is definite. Applicants, therefore, request the withdrawal of this rejection.

2. Claims 67-68, 73, 100-102, and 104-130

The Action rejected claims 67-68, 73, 100-102, and 104-130 under 35 U.S.C. § 112, second paragraph, as being indefinite for omitting essential steps. In particular, the Action alleges that a step to determine the decreased state of ACE2 is required. Although Applicants disagree that the claims are indefinite, claim 67 has been amended to recite such a step.

Independent claims 108, 116, and 125 do not recite "an ACE2 decreased state." Thus, it appears that the rejection of these claims, as well as the claims that depend from them, was made in error. In view of the above, Applicants respectfully request the withdrawal of this rejection.

D. *Conclusion*

In view of the above, Applicants believe that this is complete reply to the Office Action dated May 6, 2008. Should the Examiner have any questions, comments, or suggestions relating to this case, the Examiner is invited to contact the undersigned Applicants' representative at (512) 536-5654.

Respectfully submitted,

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Date: August 29, 2008